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PATENT
071949-2106

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re the Application of:

Kenneth F. Buechler, *et al.*

Serial No.: 09/687,051

Title: NOVEL METHODS FOR THE ASSAY OF TROPONIN I AND T AND COMPLEXES OF TROPONIN I AND T AND SELECTION OF ANTIBODIES FOR USE IN IMMUNOASSAYS

Filing Date: October 12, 2000

Group Art Unit: 1641

Examiner: Gabel, G.

CERTIFICATE OF MAILING

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January 3, 2003
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RESPONSE TO OFFICE ACTION

Commissioner for Patents
Washington, DC 20231

Sir:

In response to the Office Action mailed on October 6, 2002 ("Paper No. 12"), Applicants respectfully request reconsideration of the claimed invention in view of following remarks.

The present invention relates to antibodies that specifically bind to cardiac-specific troponin I in both free and complexed forms. In particular, the instant claims relate to antibodies that are insensitive with respect to each cardiac troponin I form selected from the group consisting of free troponin I, troponin I in binary complexes with troponin C, and troponin I in ternary complexes with troponin C and troponin T; to methods for selecting such insensitive antibodies, and to compositions using such insensitive antibodies. Such antibodies may be

provided on solid phases and as members of an antibody pair comprising a solid phase antibody and a labeled antibody. Claims 69-74 and 79-93 are currently under examination.

Non Art-Related Remarks

35 U.S.C. § 112, First Paragraph, Enablement Requirement

Applicants respectfully traverse the rejection of claims 69-74 and 79-93 under 35 U.S.C. § 112, first paragraph, in which the Examiner contends that the specification does not enable the skilled artisan to provide a single antibody having a binding specificity for each of free cardiac specific troponin I, binary complexes comprising cardiac specific troponin I, and ternary complexes comprising cardiac specific troponin I. Applicants submit that the skilled artisan could practice the claimed invention without undue experimentation.

As an initial matter, the Examiner acknowledges that the specification is enabling for assays to determine free and complexed cardiac specific isoforms of troponin using a cocktail of antibodies to provide the necessary binding specificity. Paper No. 12, page 3. In this regard, Applicants point out that claims 71-74 refer to methods for selecting two or more antibodies for use in an assay that is insensitive with respect to free cardiac specific troponin I, binary complexes comprising cardiac specific troponin I, and ternary complexes comprising cardiac specific troponin I. Likewise, claims 84, 85, 90, and 93 refer to the use of antibodies that are pools of individual antibodies. Because the Examiner appears to expressly acknowledge the enablement of these claims, Applicants respectfully request clarification of the rejection with regard to these claims.

With regard to the substance of the enablement rejection, Applicants respectfully submit that the factors set forth in *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1998) demonstrate that the present claims meet the enablement standard of 35 U.S.C. § 112, first paragraph.

Nature of the invention

The Examiner is incorrect that "the invention is directed to a cocktail of antibodies having specific binding for each one of the free, binary complex, and ternary complex... of cTnI." Paper No. 12, paragraph bridging pages 3 and 4. The present invention is directed to providing one or more antibodies that are insensitive with respect to free cardiac specific troponin I, binary complexes comprising cardiac specific troponin I, and ternary complexes comprising cardiac specific troponin I. *See, e.g.*, specification, page 6, lines 4-17; page 8, lines 9-18. The use of a "cocktail of antibodies," as referred to by the Examiner, is one embodiment of the present invention. But, as noted in both the specification and the instant claims, insensitive antibodies may be provided either as individual antibodies or as antibody cocktails. *See, e.g.*, specification, page 24, lines 21-29.

State of the prior art

The Examiner acknowledges that "the prior art of record fails to disclose [any such] antibody." Paper No. 12, page 4.

Level of one of ordinary skill

The Examiner acknowledges that "the level of skill in the art is high." Paper No. 12, page 5.

Predictability in the art

The Examiner is incorrect that "there is no predictability based on the instant specification that a single antibody has specific binding for each and all of the free, binary and ternary complexed isoforms of cTnI." Paper No. 12, page 4. Applicants respectfully submit that the Examiner' assertion of a lack of predictability is merely opinion, and is unsupported by any evidence or reasoning based on sound scientific principles. As such, the Examiner's assertion cannot support a *prima facie* case for lack of enablement. *See, e.g.*, MPEP § 2164.04 (the

Examiner bears the burden of "making specific findings of fact, supported by the evidence.... Specific technical reasons are always required).

Moreover, to provide a technical discussion of the present invention, Applicants provide herewith a declaration of Dr. Kenneth F. Buechler previously filed in copending and related U.S. Application No. 09/349,194. This declaration describes why, in contrast to the Examiner's assertions, those of ordinary skill in the art would readily acknowledge that antibodies which are insensitive with respect to the complex state of cardiac specific troponin I could be produced using only routine methods well known in the art.

As described in paragraph 4 of the Buechler declaration, cardiac specific troponin Troponin I contains certain antigenic sites that are "cardiac specific," and antibodies directed to these sites may be used to determine cardiac specific troponin I from non-cardiac troponin I. As further described in paragraphs 5 and 6, certain of these cardiac specific sites may be obscured in binary and ternary complexes of the cardiac specific troponin isoforms. Thus antibodies to these sites may be used to specifically identify the free form, the binary complex form, or the ternary complex form of the troponin isoform.

Certain other cardiac specific sites, however, may remain available for antibody recognition even when troponin I is complexed with other troponin isoforms. Such sites can provide an epitope through which a single antibody can provide specific binding for each and all of the free, binary and ternary complexed isoforms. As noted by Dr. Buechler in paragraph 7 of the declaration, this point is clearly brought home to the skilled artisan in the instant specification, *e.g.*, on page 24, lines 21-29.

Amount of direction or guidance present

Applicants also respectfully disagree that "the specification fails to provide any guidance to provide a single antibody that specifically binds all of the free, binary and ternary complexed isoforms of cTnI." Paper No. 12, page 4, last full paragraph. In fact, the specification describes methods for obtaining antibodies that are insensitive to the complex state of cardiac specific

troponin isoforms, *e.g.*, on page 21, line 3, through page 22, line 19. As described in this section, purified troponin complexes may be used as immunogens in mice or rabbits to prepare monoclonal or polyclonal antibodies, which may be screened for complex-insensitive antibodies for use in the claimed assay methods.

Presence of working examples

Applicants also respectfully disagree that "[t]here are no working examples that show... results using a single antibody." Paper No. 12, paragraph bridging pages 4 and 5. As discussed by Dr. Buechler in paragraph 8 of the declaration, Example 10 describes certain antibodies that were demonstrated to bind both free and binary complexes of cardiac specific troponin I equally well. *See, e.g.*, specification, page 63, lines 20-26. Applicants note that a single biotinylated antibody, and a single labeled antibody, are used in these assays, which rely on formation of a sandwich of (labeled antibody)-(analyte)-(biotinylated antibody)-(avidin solid phase) for development of an assay signal. Specification, page 62, lines 20-24. The skilled artisan would understand that both the biotinylated and labeled antibodies must each bind to both free and binary complexes of troponin I in order for the described assays to measure both free and binary complexes of troponin I.

Similarly, in Example 23 beginning on page 87, the specification describes assays able to measure both free and ternary complexes of troponin I. As noted on page 89, lines 20-23, labeled and biotinylated antibody pairs could be identified that provide assay responses that are insensitive to the complex state of troponin I. Again, because these assays rely on formation of a sandwich of (labeled antibody)-(analyte)-(biotinylated antibody)-(avidin solid phase) for development of an assay signal, the skilled artisan would understand that both the biotinylated and labeled antibodies must each bind to both free and ternary complexes of troponin I.

Quantity of experimentation necessary

Applicants further disagree with the Examiner's unsupported assertion that "it would require undue amount of experimentation for the skilled artisan to make and use the method as

claimed." Paper No. 12, page 5. As noted by Dr. Buechler in paragraph 3 of the declaration, methods for identifying antibodies that are insensitive to the complex state of cardiac specific troponin isoforms are described in detail in the instant specification. Moreover, as noted by the Examiner, the level of skill in the art for producing antibodies and formulating assay methods is high. Applicants respectfully submit that methods for producing antibodies have long been well known and routine to those of skill in the art. *See, e.g., Hybritech Inc. v. Monoclonal Antibodies, Inc.*, 231 USPQ 81, 94 (Fed. Cir. 1986) (agreeing that "the method for producing monoclonal antibodies in vitro was well known prior to [1980]." The fact that experimentation may be complex does not make it undue if, as in the present case, the art typically engages in such experimentation. MPEP § 2164.01.

The instant claims meet the enablement standard of 35 U.S.C. § 112, first paragraph

Considering the teachings of the specification, Dr. Buechler concludes that the skilled artisan could indeed provide a single antibody population having a binding specificity for each of free cardiac specific troponin I, binary complexes comprising cardiac specific troponin I, and ternary complexes comprising cardiac specific troponin I, using only the teachings of the instant specification as filed, together with methods that are routine and well known in the art. *See, e.g.*, Buechler declaration, paragraph 3.

In view of this objective evidence of enablement, and the foregoing discussion of the various *Wands* factors cited by the Examiner in the office action, Applicants respectfully submit that one of ordinary skill in the art could make and use the claimed invention using the specification as a guide without undue experimentation. Applicants, therefore, request that the rejection under 35 U.S.C. § 112, first paragraph, be reconsidered and withdrawn.